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Dyspnoea, cyanosis and digital clubbing in a 28-year-old patient as a result of hepatopulmonary syndrome

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Abstract

This paper presents a case of a young patient with cyanosis and digital clubbing, until then an active, sporty person. He sought medical assistance due to the growing dyspnoea and the drop of effort tolerance. Initially the diagnostic process focused on the confirmation of the suspicion of pulmonary fibrosis or another interstitial lung disease as causes of the respiratory failure. Due to the atypical presentation of the symptoms, reaching the final diagnosis of digestive system disease with lung involvement required a more thorough multifaceted diagnostics of a number of systems and organs.

Key words: dyspnoea, finger clubbing, cyanosis, hepatopulmonary syndrome

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Introduction

Digital clubbing and cyanosis are symptoms of anoxaemia and changes in the circulatory system and tissues that correspond to it. They bring associations with a long-term disease process, which in the course of time leads to the defect of haemoglobin oxygenation and deviations in the physical examination of the patient. Rarely are these changes described in young people. Due to their uniqueness they require that numerous potential diseases should be taken into account. Besides a number of neoplastic diseases (lung cancer, metastatic disease with lesions in lungs, hematologic malignancies), they can occur in the course of heart diseases (cyanotic heart defects, arteriovenous malformations, endocarditis), diseases of the respiratory system (interstitial pneumonitis, bronchiectasis), diseases of the digestive

system (Crohn's disease, ulcerative colitis, liver cirrhosis), diseases of the endocrine system (hyperthyroidism) and diseases of the connective tissue [1]. Owing to the probably multidisciplinary etiology of the lesions, the differential diagnosis requires a number of laboratory tests, as well as imaging and endoscopic examinations in order to eliminate concomitant disorders.

This study presents a case of a young patient with cyanosis and digital clubbing, till then an active, sporty person. He sought medical assistance due to the growing dyspnoea and the drop of effort tolerance. Initially the diagnostic process focused on the confirmation of the suspicion of pulmonary fibrosis or another interstitial lung disease as causes of the respiratory failure. Due to the atypical presentation of the symptoms, reaching the final diagnosis required a more thorough multifaceted diagnostics of a number of systems and organs.

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Case study

The patient aged 28 reported in March 2009 in the Internal Diseases Ward due to the reduction of the effort tolerance growing for the previous six months, with the concurrent dyspnoea, cough, and loss of the body weight. Until then the patient had been an active person, a lawn tennis player. As of the moment of reporting to the ward, walking a distance of several dozen metres caused dyspnoea that required rest. The professional history of the patient did not mention any exposures to chemical substances, dusts and gases. Due to an injury in the area of the hip joint with the consequential bone necrosis, the patient had undergone the hip replacement procedure in April 2006.

At admission, confirmed deviations from the normal condition included central cyanosis and digital clubbing. What attracted attention was the accelerated heart rate to ca. 110 per minute, at normal values of the blood pressure.

Lab tests revealed polyglobulia with the haemoglobin concentration of 19.2 g/dl, leukopenia $3 \times 10^3/\text{dl}$, thrombocytopenia $69 \times 10^3/\text{dl}$, increased GGTP activity to 194 U/l. Serological tests for detection of viral infections (HBs antigen, anti-HCV antibodies, 4th generation HIV combo test) revealed no deviations. The arterial blood gases analysis revealed hypoxemia (partial pressure of oxygen (pO_2) 50 mm Hg) with the reduction of the blood saturation to 86% and partial pressure of carbon dioxide (pCO_2) of 27 mm Hg. The diagnostics was completed with a number of imaging examinations of the patient's chest and abdominal cavity. In the chest radiograph, besides an intensified vascular pattern and pleural thickening in the lung apices, no other deviations were revealed. As a result of the computed tomography (CT) angiography of the pulmonary arteries, pulmonary embolism was excluded; nevertheless, in the fragmentarily covered abdominal cavity structures which might correspond to thickened veins were demonstrated. Furthermore, fibrous lesions of top segments of the lower and upper lobes of both lungs were discovered. The abdominal ultrasonography (USG) and the echocardiography tests did not reveal any lesions.

Due to the lesions described in the CT angiography, an endoscopic examination of the upper part of the digestive tract was performed, revealing slightly thickened veins of the oesophagus, erosive gastritis, and insufficiency of the stomach cardia.

As it was impossible to determine the source of the patient's condition, he was referred to the

specialist respiratory hospital with the diagnosis of chronic respiratory failure for further diagnostics.

The blood count tests and biochemical tests carried out in the specialist hospital confirmed the deviations revealed in the internal diseases ward. Due to the haematological parameters, a bone marrow biopsy, a proteinogram, and a screening test towards antinuclear antibodies (ANA) were performed. In the myelogram features of the activation of the red blood cells were demonstrated, but no features of a neoplastic infiltration were revealed. The result of the proteinogram remained within normal limits. The examination towards ANA did not reveal the presence of antinuclear antibodies.

In the repeated USG examination of the abdominal cavity the ultrasonographer described thickened blood vessels of the hilum of the spleen.

The bronchofiberoptic examination was performed, which revealed congestion of the mucous membrane of the bronchi, with numerous thickened winding vessels. Material was taken in order to carry out cytological, bacteriological (also towards tuberculosis), mycological, and bronchoalveolar lavage (BAL) cytology tests. In the material no pathogenic bacteria, no *Mycobacterium tuberculosis*, no fungi and no neoplastic cells were revealed. The cell pattern of BAL remained within the normal limits.

The function tests of the respiratory system did not reveal any significant ventilation disorders in spirometry; in the CO diffusion test (DLCO), however, the lowering of this parameter to 41% of the due value was confirmed.

Measurements of the blood saturation were taken in the supine and standing positions and demonstrated orthodeoxy.

Due to the orthodeoxy, the echocardiographic examination was repeated and supplemented with the intravenous injection of shaken saline. Air bubbles appeared in the left half of the heart after 4 cycles of the heart activity, which corresponds to echocardiographic features of the extracardiac leak (Fig. 1).

Due to the fact that chronic hypoxia with orthodeoxy, features of impaired diffusion in the lungs, the extracardiac leak along with a set of deviations which might be suggestive of liver damage had been revealed (drop in the number of thrombocytes and leukocytes, presence of oesophageal varices), a suspicion of the hepatopulmonary syndrome (HPS) was formulated. The patient was qualified to home oxygen therapy, the oxygen flow optimal for the normalisation

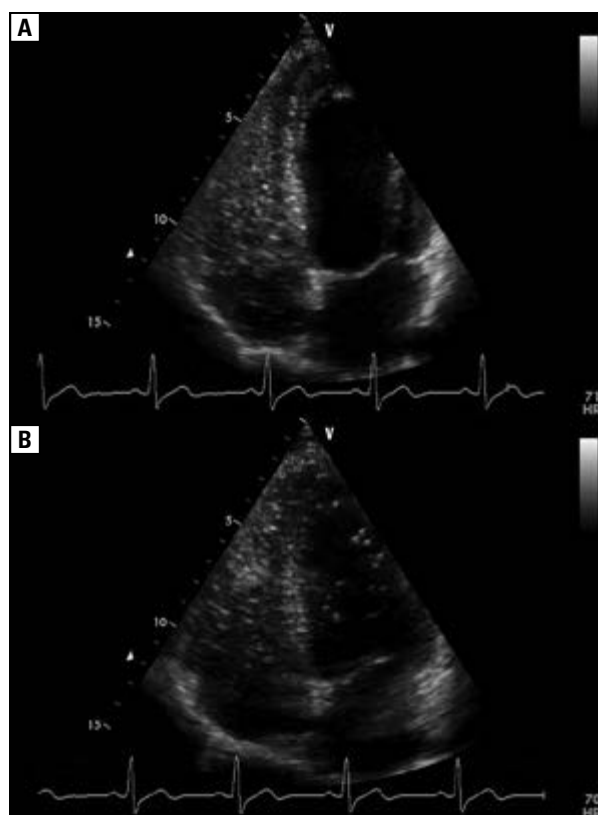


Figure 1. Echocardiogram. **A** — Contrast in the right part of the heart; **B** — contrast in both parts of the heart after 4 cycles of heart activity

of the gasometric parameters was determined; the patient was referred to the consulting centre of home oxygen therapy, where he received the oxygen concentrator. Consultations with the gastroenterology and hepatology specialist hospital were carried out and the date of admitting the patient for the purposes of further hepatologic diagnostics was set.

The tests carried out in the gastroenterological specialist hospital did not reveal any features of autoimmune hepatitis, hemochromatosis or Wilson's disease, features of liver damage caused by the Epstein-Barr virus, cytomegalovirus and Herpes Simplex virus infection (May 2009).

Imaging examinations of the abdominal cavity (USG and magnetic resonance) revealed thickened vessels of the spleen hilum, features of intensified collateral perisplenic and perirenal circulation, especially on the left kidney side, features of heterogeneous hepatic perfusion, and poor flow in the portal vein and in the splenic vein – the radiologist who described the results suggested indirect features of past thrombosis of these vessels.

In order to confirm the diagnosis of the HPS the albumin scintigraphy was performed. The

perfusion imaging revealed varying saturation of the right lung, distribution of the radiotracer in the central nervous system, kidneys, thyroid, and the digestive system. The calculated index of the right-left leak equalled 42% (value that excludes HPS — below 6%). The examination confirmed the extracardiac right-left leak suspected on the basis of the echocardiographic examination.

Liver biopsy was performed, on the basis of which features of fibrosis of the 3rd and 4th degree were confirmed.

On the basis of the clinical picture and the additional tests performed, liver cirrhosis of unknown etiology was diagnosed, with respiratory failure in the course of the hepatopulmonary syndrome.

Due to the overall clinical picture, the process of qualifying the patient to the hepatic transplantation was commenced. In the course of qualification the presence of anti-HBc antibodies was detected, indicating past viral B hepatitis as the probable cause of the liver cirrhosis.

The patient was presented on an interdisciplinary council, which qualified him to the hepatic transplantation.

The hepatic transplantation was performed in the specialist hospital of general, transplant and liver surgery in January 2010, 15 months after the symptoms of the respiratory failure had commenced in the patient. The procedure itself and the postsurgical period was with no complications. In the post-transplantation period the respiratory failure persisted and the patient still required further oxygen therapy. The patient was discharged home with recommendations to take immunosuppression drugs (Prednisone in the dose of 15 mg, Tacrolimus 6 mg in two divided doses), anticoagulants (Nadroparin 3800 units twice a day), antimicrobial agents (Trimethoprim, Sulphamethoxazole, Aciclovir, Fluconazole), Omeprazole, Furosemide, calcium and magnesium supplementation, and oxygen therapy continuation. Further pulmonological and transplantation follow-up was planned.

One month after the transplantation the patient reported to the Emergency Room complaining about pain in his chest. Based on the ECG examination and measurements of cardiac markers, acute coronary syndrome was excluded as a potential cause of the pain. The biochemical tests performed revealed hyponatremia of 121 mmol/l. The patient was admitted to gastroenterological specialist hospital, where the concentration of sodium was normalised by means of the fluid therapy. Furthermore, the intake of

Table 1. Control parameters in the respiratory system function tests

Date/ /measurement	05.2009	03.2010	06.2010	09.2010	05.2011	01.2012	29.01.2013
pO ₂ atmospheric oxygen, sitting position [mm Hg]	51.1	49.7	72.2	78,4	108	131	124
pO ₂ atmospheric oxygen, supine position [mm Hg]	Not determined	56.2	70.7	114	115	131	119
pO ₂ at FiO ₂ 1.0 [mm Hg]	Not determined	250	234	440	386	Not determined	391
DLCO [value due]	41%	28%	Not determined	Not determined	66%	63%	52.7%
6MWT [m]	Not determined	465	600	685	750	790	705
6MWT saturation before ≥ after	Not determined	80% ≥ 57%	91% ≥ 77%	97% ≥ 86%	97% ≥ 84%	97% ≥ 87%	97% ≥ 88%

6MWT — 6 minute walk test

Fluconazole was discontinued and the dose of Tacrolimus was reduced under the control of the concentration in serum. The episode of hyponatremia was most probably connected with the increase of the concentration of Tacrolimus in blood due to the suppression of CYP35 enzyme by Fluconazole.

The patient remained under constant pulmonological control and the supervision of the consulting centre of home oxygen therapy. The successively performed check-ups of the functions of the respiratory system (Table 1) point out to a slow increase of the value of the partial pressure of oxygen, which six months after the transplantation (June 2010) exceeded 60 mm Hg. The value of diffusion increased from the lowest described 28% of the normal value to ca. 60%. The distance in the test of the 6-minute walk increased considerably; nevertheless, a significant drop in saturation after exercise was observed at the value of 10%. Considering the above, contrast echocardiography was performed. No features of leak were revealed at rest, during the Valsalva maneuver single bubbles of the contrast agent were observed after 3 cycles of the heart activity. The patient was diagnosed as suffering from the intrapulmonary vascular dilatation syndrome after the hepatic transplantation for liver cirrhosis.

Due to the improvement of the arterial blood gases parameters and increasing tolerance of effort, the patient required only periodical application of the oxygen concentrator. The patient returned to his professional work. Due to the gasometric values, their stabilisation after the hepatic transplantation, the patient returned the

oxygen concentrator (12.2015) — the cause of the respiratory failure had ceased.

Discussion

Liver cirrhosis has its influence on all organ systems of the human organism, including hemodynamic parameters and the gas exchange in lungs. Hepatopulmonary syndrome is a pulmonary complication of the liver disease connected with the defect of blood oxygenation in the vascular bed of lungs. Although the first case was described in 1884, the term HPS was introduced only in 1977 by Kennedy. It is also combined with the occurrence of portal hypertension; however, this syndrome can be caused by every chronic disease of the liver, as well as some causes of acute liver damage [2–4]. In the subject literature HPS is estimated to be 4% to 32% of adult patients with the end-stage liver disease. In the population of children this refers to 9–20%. The most frequent liver pathology that leads to HPS is liver cirrhosis; nevertheless, the course and manifestation of the syndrome does not depend on the root cause of the liver damage. The development of HPS has been described in the course of the Budd-Chiari syndrome, in portal hypertension without any chronic liver disease, as well as in liver diseases without concomitant cirrhosis and portal hypertension [5, 6]. The syndrome is defined as the concurrence of a triad of symptom: liver damage which may be concomitant with portal hypertension, hypoxemia resulting from the disorders in the ventilation to perfusion ratio, and thickening of the intrapulmonary

vascular bed [2, 7]. Pathophysiology of disorders in the pulmonary circulation has not been fully clarified yet; nevertheless, there is a body of evidence confirming the role of mediators with vasoactive properties, such as nitric oxide (NO), or the tumour necrosis factor α (TNF- α). The role of accumulation of macrophages stimulated by the increase of the concentration of endotoxins caused by the deterioration of the liver functions has been postulated, as well. Substances with the angiogenic potential produced by macrophages cause the increase of the number of capillaries and stimulate intervacular connections [3, 5, 7].

Depending on the author, the dissemination of HPS is estimated in quite broad limits. This results from the fact that the precise definition of HPS remains subject of controversies and different authors adopt different cut-off points for diagnostic criteria. In the latest guidelines from 2016 the International Liver Transplantation Society recommends that the oxygenation defect should be defined in compliance with the criteria proposed by the European Respiratory Society (ERS) as an alveolar-arterial gradient at the level of at least 15 mm Hg. It is recommended to adopt the value of 20 mm Hg as the minimum value for the group of patients above 64 years of age [8, 9]. In the patient described herein the gradient equalled 67 mm Hg. The intensification of HPS is categorised on the basis of the partial concentration of oxygen in arterial blood. This division distinguishes 4 degrees. In the patient described herein the value of pO_2 at the level of 49 mm Hg classifies him in the fourth — the highest — stage [3]. This value along with the diagnosis of liver cirrhosis obliges to commence the qualification process leading to the liver transplantation.

The standard for the diagnostic screening in order to reveal the extracardiac blood leak is the transthoracic echocardiography with contrast obtained by means of shaken saline. In the case of normal vessels of the pulmonary vascular bed, when the contrast becomes visible in the left part of the heart, it is stopped in the pulmonary alveoli. In HPS the occurrence of contrast bubbles above 3 cycles of the activity of the heart after they become visible in the left part of the heart is characteristic, as it was confirmed in our patient. Abrams in his work dated 1995 suggests regarding the lack of leak features in the transthoracic echocardiography as the HPS exclusion criterion [10, 11]. An alternative test seems to be the examination of perfusion by means of technetium (^{99m}Tc) macroaggregated albumin and the comparison of its distribution in the brain and in lungs. The

drawback of this test is the impossibility of differentiating between the intra- and extracardiac leak; nevertheless, in the event of a concomitant lung disease with hypoxemia it constitutes a significant indicator of the participation of the HPS component in the gas exchange balance disorders. Furthermore, a high leak factor in the perfusion test (defined as the value exceeding 20%, at $pO_2 < 50$ mm Hg) according to some authors has a positive correlation with the increase of the mortality rate after liver transplantation and can be used as a guideline referring to the steps to be undertaken after the transplantation [10]. The examination of the effectiveness of diagnostic strategies revealed that the most cost-effective can be additional use of pulse oximetry as the first screening element before imaging examinations [12]. In the patient described herein during the diagnostic process the blood saturation was determined, and then echocardiography and perfusion tests were performed. The results obtained confirmed the extracardiac leak with a high leak factor, indicating the risk of complications in the post-transplantation period. Oxygen supplementation is the first therapeutic option proposed to HPS patients. The main assumption for the adoption of this method is the control of the symptoms, because the presence of the leak hampers the appropriate correction of gasometric disorders [8, 13]. In the case described herein, the patient was qualified to home oxygen therapy on the basis of the rules applied in other diseases with the respiratory failure. Despite the described high leak factor, full compensation of the respiratory failure was successfully obtained ($pO_2 > 60$ mm Hg) without any significant retention of carbon dioxide. Another treatment taken into consideration is the adoption of portosystemic anastomosis with the objective to reduce the pressure in the basin of the portal vein. The available subject literature covers casuistic works and small groups of patients with a short period of observations after the procedure. The results obtained are contradictory, as of today there are no clear-cut criteria that would allow to isolate a group of patients with HPS obtaining measurable benefits by the application of the vascular anastomosis. [14–16] As a palliative procedure, embolisation of thickened vessels or local resections of the pulmonary tissue that contains them is adopted [7]. In connection with the values obtained in gasometry in the patient described herein, the patient was directly qualified to lung transplantation as the target treatment.

Despite the fact that HPS is an indication for liver transplantation, it also constitutes a risk

factor of postoperative complications. The death hazard ratio in patients with HPS compared to patients without HPS equals 2.41 [17]. In patients with HPS in the period that directly follows the surgery rapid deterioration of gasometric parameters may occur, which is probably connected with the blood flow redistribution. Despite the fact that it is a reversible phenomenon, it may contribute to death in the post-operative period. It correlates with a low value of pO_2 obtained before the surgery during breathing with the atmospheric air, which occurred in the described patient [18].

A separate issue is the reversibility of the oxygenation defect after the liver transplantation. In more than a half of the patients in the group described by French researchers in the early post-operative period gas exchange disorders persisted; they did not, however, correlate with the general post-operative mortality. In 15 out of 21 patients the period of 6 subsequent months brought about an improvement in terms of oxygenation (defined as the increase of pO_2 above 70 mm Hg). The average period over which the patients required the oxygen treatment reached 3 months after the transplantation [18] in the patient described herein the improvement criteria described above were satisfied over the period of 5 months after the liver transplantation. In spite of this, residual features of thickening of the pulmonary vessels persisted.

From amongst the symptoms through which HPS manifests itself, the most frequent one is effort dyspnoea, occurring in 80% of cases. Much less frequent symptoms are chest pain and fainting [19]. From the group of signs, lesions characteristic for liver diseases, such as spider angioma or palmar erythema, or changes connected with the portal hypertension, such as e.g. ascites and splenomegalia, can be observed. Over time physical manifestations of the blood oxygenation defect appear, such as digital clubbing or central cyanosis [19, 20].

Summing up, the hepatopulmonary syndrome is a rare cause of oxygenation disorders. If there are no significant deviations in examinations performed within the scheme of dyspnoea diagnostics, it is recommended to perform basic screening tests towards this syndrome (standing and supine saturation measurement, echocardiography with the intake of shaken saline), even if there are no signs of the syndrome, or no history that would be suggestive of potential liver damage.

Conflict of interest

The authors declare no conflict of interest.

References:

- Dubrey S, Pal S, Singh S, et al. Digital clubbing: forms, associations and pathophysiology. *Br J Hosp Med (Lond)*. 2016; 77(7): 403–408, doi: [10.12968/hmed.2016.77.7.403](https://doi.org/10.12968/hmed.2016.77.7.403), indexed in Pubmed: [27388379](https://pubmed.ncbi.nlm.nih.gov/27388379/).
- Zulkifli A, Hilman Zulkifli A, Nadim Marchian T. Hepatopulmonary syndrome: a brief review. *Rom J Intern Med*. 2016; 1–11.
- Rodríguez-Roisin R, Krowka MJ, Hervé Ph, et al. ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee. Pulmonary-Hepatic vascular Disorders (PHD). *Eur Respir J*. 2004; 24(5): 861–880, doi: [10.1183/09031936.04.00010904](https://doi.org/10.1183/09031936.04.00010904), indexed in Pubmed: [15516683](https://pubmed.ncbi.nlm.nih.gov/15516683/).
- Kennedy TC, Knudson RJ. Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis. *Chest*. 1977; 72(3): 305–309, indexed in Pubmed: [891282](https://pubmed.ncbi.nlm.nih.gov/891282/).
- Tumgor G. Cirrhosis and hepatopulmonary syndrome. *World J Gastroenterol*. 2014; 20(10): 2586–2594, doi: [10.3748/wjg.v20.i10.2586](https://doi.org/10.3748/wjg.v20.i10.2586), indexed in Pubmed: [24627594](https://pubmed.ncbi.nlm.nih.gov/24627594/).
- Mokhtarifar A, Azimi H, Esmaeelzadeh A, et al. Frequency of Hepatopulmonary Syndrome (HPS) Among Patients With Liver Cirrhosis: A Letter to Editor. *Hepat Mon*. 2016; 16(2): e35990, doi: [10.5812/hepatmon.35990](https://doi.org/10.5812/hepatmon.35990), indexed in Pubmed: [27148388](https://pubmed.ncbi.nlm.nih.gov/27148388/).
- Cosarderelioglu C, Cosar AM, Gurakar M, et al. Hepatopulmonary Syndrome and Liver Transplantation: A Recent Review of the Literature. *J Clin Transl Hepatol*. 2016; 4(1): 47–53, doi: [10.14218/JCTH.2015.00044](https://doi.org/10.14218/JCTH.2015.00044), indexed in Pubmed: [27047772](https://pubmed.ncbi.nlm.nih.gov/27047772/).
- Krowka MJ, Fallon MB, Kawut SM, et al. International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. *Transplantation*. 2016; 100(7): 1440–1452, doi: [10.1097/TP.0000000000001229](https://doi.org/10.1097/TP.0000000000001229), indexed in Pubmed: [27326810](https://pubmed.ncbi.nlm.nih.gov/27326810/).
- Stoller JK, Lange PA, Westveer MK, et al. Prevalence and reversibility of the hepatopulmonary syndrome after liver transplantation. The Cleveland Clinic experience. *West J Med*. 1995; 163(2): 133–138, indexed in Pubmed: [7571560](https://pubmed.ncbi.nlm.nih.gov/7571560/).
- Machicao VI, Balakrishnan M, Fallon MB. Pulmonary complications in chronic liver disease. *Hepatology*. 2014; 59(4): 1627–1637, doi: [10.1002/hep.26745](https://doi.org/10.1002/hep.26745), indexed in Pubmed: [24089295](https://pubmed.ncbi.nlm.nih.gov/24089295/).
- Abrams GA, Jaffe CC, Hoffer PB, et al. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. *Gastroenterology*. 1995; 109(4): 1283–1288, indexed in Pubmed: [7557096](https://pubmed.ncbi.nlm.nih.gov/7557096/).
- Roberts DN, Arguedas MR, Fallon MB. Cost-effectiveness of screening for hepatopulmonary syndrome in liver transplant candidates. *Liver Transpl*. 2007; 13(2): 206–214, doi: [10.1002/lt.20931](https://doi.org/10.1002/lt.20931), indexed in Pubmed: [17205561](https://pubmed.ncbi.nlm.nih.gov/17205561/).
- Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome—a liver-induced lung vascular disorder. *N Engl J Med*. 2008; 358(22): 2378–2387, doi: [10.1056/NEJMra0707185](https://doi.org/10.1056/NEJMra0707185), indexed in Pubmed: [18509123](https://pubmed.ncbi.nlm.nih.gov/18509123/).
- Corley DA, Scharschmidt B, Bass N, et al. Lack of efficacy of TIPs for hepatopulmonary syndrome. *Gastroenterology*. 1997; 113(2): 728–730, indexed in Pubmed: [9247498](https://pubmed.ncbi.nlm.nih.gov/9247498/).
- Paramesh AS, Husain SZ, Shneider B, et al. Improvement of hepatopulmonary syndrome after transjugular intrahepatic portosystemic shunting: case report and review of literature. *Pediatr Transplant*. 2003; 7(2): 157–162, indexed in Pubmed: [12654059](https://pubmed.ncbi.nlm.nih.gov/12654059/).
- Tsauo J, Weng N, Ma H, et al. Role of Transjugular Intrahepatic Portosystemic Shunts in the Management of Hepatopulmonary Syndrome: A Systemic Literature Review. *J Vasc Interv Radiol*. 2015; 26(9): 1266–1271, doi: [10.1016/j.jvir.2015.04.017](https://doi.org/10.1016/j.jvir.2015.04.017), indexed in Pubmed: [26074026](https://pubmed.ncbi.nlm.nih.gov/26074026/).
- Fallon MB, Krowka MJ, Brown RS, et al. Pulmonary Vascular Complications of Liver Disease Study Group. Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. *Gastroenterology*. 2008; 135(4): 1168–1175, doi: [10.1053/j.gastro.2008.06.038](https://doi.org/10.1053/j.gastro.2008.06.038), indexed in Pubmed: [18644373](https://pubmed.ncbi.nlm.nih.gov/18644373/).
- Taillé C, Cadranet J, Bellocq A, et al. Liver transplantation for hepatopulmonary syndrome: a ten-year experience in Paris, France. *Transplantation*. 2003; 75(15): 1482–1489.
- Medarov BI, Chopra A, Judson MA. Clinical aspects of portopulmonary hypertension. *Respir Med*. 2014; 108(7): 943–954, doi: [10.1016/j.rmed.2014.04.004](https://doi.org/10.1016/j.rmed.2014.04.004), indexed in Pubmed: [24816204](https://pubmed.ncbi.nlm.nih.gov/24816204/).
- Ramalingam VS, Ansari S, Fisher M. Respiratory Complication in Liver Disease. *Crit Care Clin*. 2016; 32(3): 357–369, doi: [10.1016/j.ccc.2016.03.002](https://doi.org/10.1016/j.ccc.2016.03.002), indexed in Pubmed: [27339676](https://pubmed.ncbi.nlm.nih.gov/27339676/).